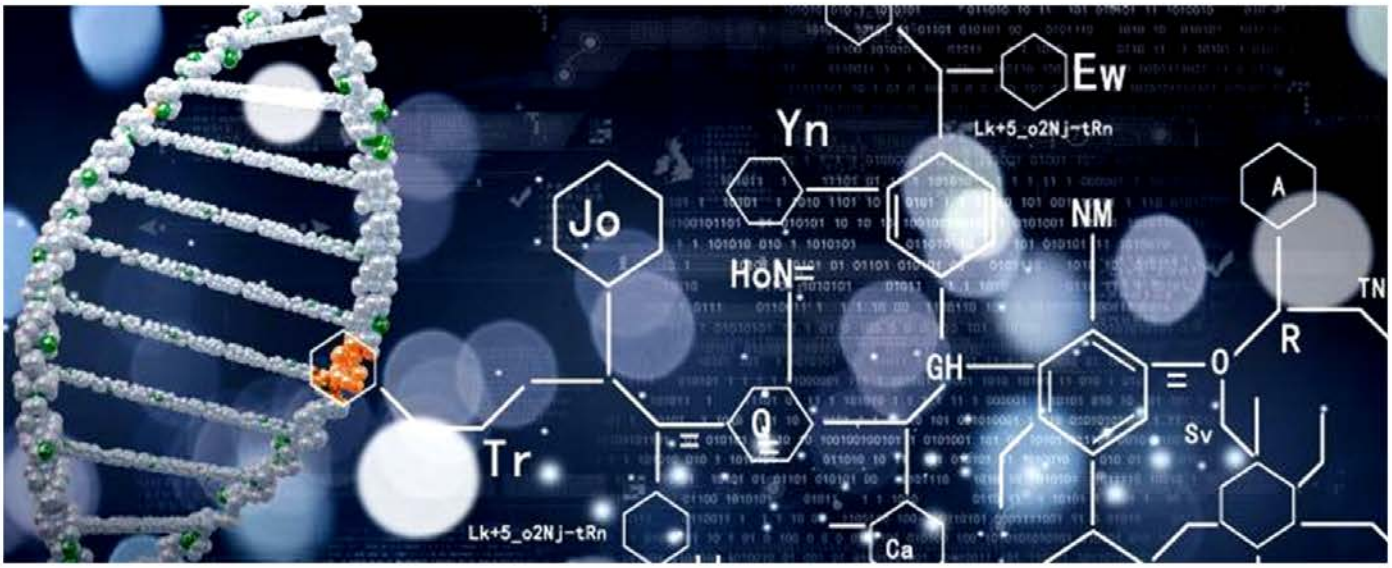
DAVINCI MEDICAL ACADEMY

SUBJECTS IN NUTSHELL FOR EFFECTIVE REVISION



BIOCHEMISTRY IN NUTSHELL

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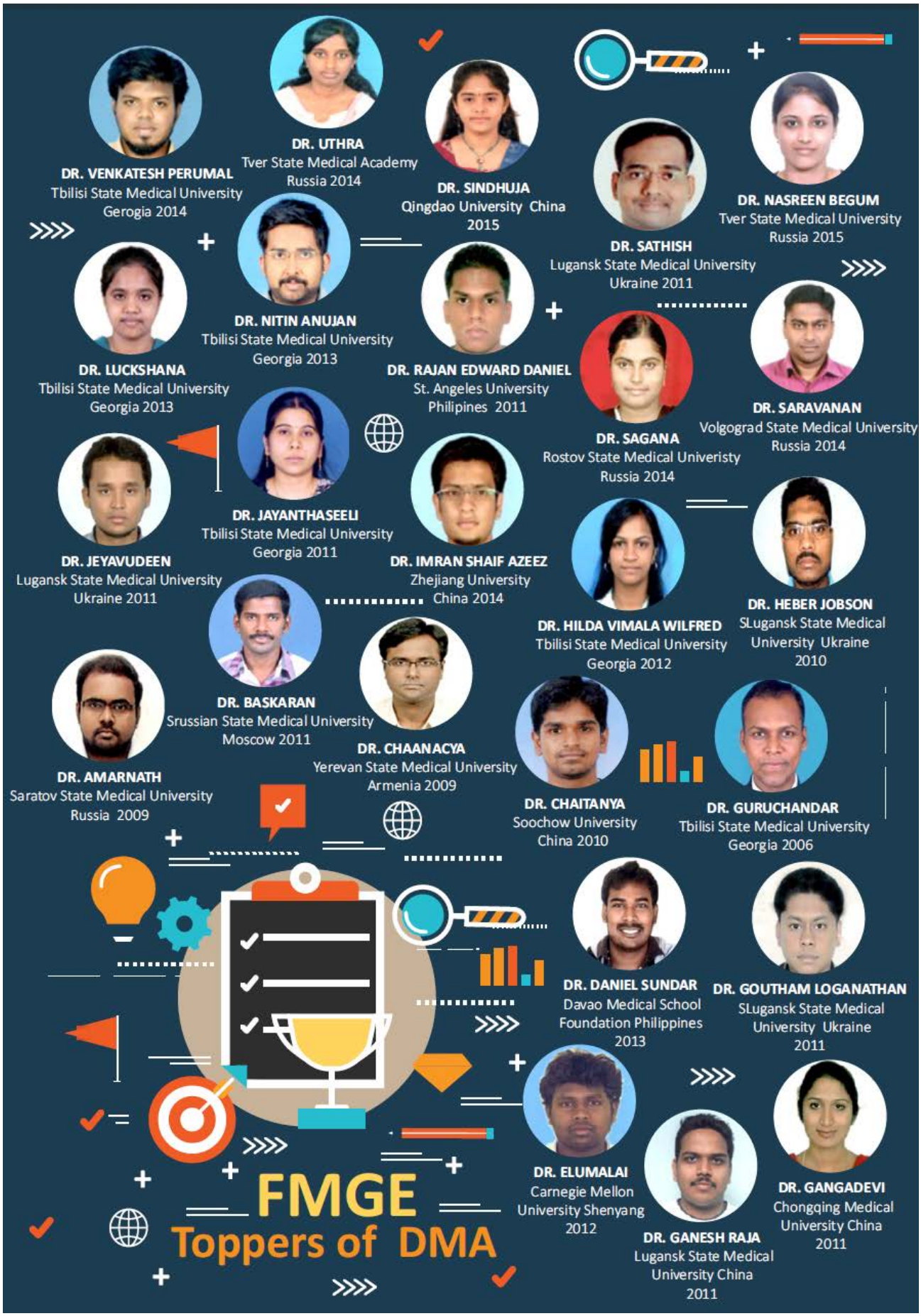
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Toppers of DMA

DMA'S CORNER OF WISDOM

1. GENERAL BIOCHEMISTRY

Oxidation	Reduction
• Loss of electrons • Addition of oxygen • Removal of hydrogen	• Gain of electrons • Removal of oxygen • Addition of hydrogen

ENZYMES

PROPERTIES OF ENZYMES

- protein catalysts
- increases the velocity of a chemical reaction
- not consumed during the reaction they catalyze
- Some types of RNAcan act like enzymes catalyzing the cleavage and synthesis of phosphodiester bonds
- RNAs with catalytic activity are called **ribozymes**

Active sites

- Enzyme moleculescontain a special pocket of cleft called the active site
- contains **amino acid side chains** create a **three-dimensional surface** complementary tothe substrate
- active sitebinds the substrateforming an enzyme substrate (ES) complex
- ES is converted to enzyme-product (EP),which subsequently dissociates to enzyme and product.

Catalytic efficiency

- Most enzyme-catalyzed reactions
- highly efficient
- proceeding from 10^3 to 10^8 times
- faster than uncatalyzed reactions
- Typically, each enzyme molecule each secondcapable of transforming **100 to 1000 substratemolecules** into product
- number of molecules of substrate converted to productper enzyme moleculeper second**called the turnover number.**

Specificity

- Enzymes are **highly specific**interacting with **one or a few substrates**catalyzing **only one type** of chemical reaction.

Cofactors

- Some enzymes associate with a nonprotein cofactorneeded for enzymic activity
- Commonly encountered cofactors include**metal ions** such as**Zn^{2+} or Fe^{2+}**
- ,organic molecules-- known as **coenzymes**often derivatives of vitamins
- Coenzyme**NAD^+** contains niacin, **FAD** contains riboflavin, coenzyme A contains **pantothenic acid.**
  - Holoenzyme refers toenzyme with its cofactor
  - Apoenzyme refers to appropriate cofactor
    - ✓ does not show biologic activity
    - ✓ prosthetic group
    - ✓ a tightly bound coenzymethat does not dissociate from the enzymefor example, the biotin bound to car boxylases

Regulation

- Enzyme activity can be regulatedenzymes can be activated or inhibited so that the **rate or product formation**responds to the **needs of the cell.**

Location within the cell

- Many enzymes are localized in specificorganelles within the cell
- Such **compartmentalization**serves to isolate the reaction substrate orproduct from other competing reactions.
- Providesa **favorable environment** for the reaction
- organizes the thousands of enzymes present inthe cell into**purposeful pathways.**

HOW ENZYMES WORK

- **first perspective**treat catalysis in terms of energychangesthat occur during the reaction
- enzymes provide an**alternate,energetically favorable reaction pathway** different from theuncatalyzedreaction
- **second perspective**how the active sitechemicallyfacilitates catalysis.

Energy changes occurring during the reaction

- Virtually all chemical reactions have an energy barrierseparating the reactants and the products
- This barriercalled the **free energy of activationenergy difference**between that of the reactants and a high-energy intermediate**occurs** during the formation of product

Free energy of activation

- peak of energy-the difference in free energy between the **reactant and T** where the high-energy intermediate is formed **duringthe conversion of reactant** to product
- Because of the high free energy of activationrates of uncatalyzedchemical reactions are **often slow.**

FACTORS AFFECTING REACTION VELOCITY

- **Substrate concentration**
- **Maximal velocity**
  - ✓ rate or velocity of a reaction
  - ✓ number of substrate molecules converted toproduct **per unit time**
  - ✓ velocity is usually expressed as **mol of product formed per minute.**
- rate of an enzyme-catalyzed reaction increase with substrate concentrationuntil a **maximal velocity (Vmax)** is reached

Hyperbolic shape of the enzyme kinetics curve

- most enzymes show **Michaelis-Mentenkinetics**
- plot of **initial reaction velocity, vo**against **substrate concentration [s],hyperbolic**
- In contrast**allosteric enzymes** frequently show a sigmoidal curvesimilar in shape to the oxygen-dissociation curve ofhemoglobin

Temperature

Increase of velocity with temperature:

- reaction velocity increases with temperatureuntil a peak velocity is reached
- increase is the result of the**increased number of molecules**having sufficientenergy to pass overthe energy barrie rform the products of the reaction.

Decrease of velocity with higher temperature

- Further elevation of the temperature
- temperature-induced **denaturation** of the enzyme results in a **decrease** in reaction velocity

PH

Effect of pH on the ionization of the active site:

- concentration of H+affects reaction velocity in several ways
- catalytic activity
- require that an amino group of the enzyme be inprotonated form (-NH3+).
- At **alkaline pH**this group is deprotonated,rate of the reaction, therefore, declines.

Effect of pH on enzyme denaturation:

- Extremes of pHlead to denaturation of the enzyme becausestructure of the catalytically active protein molecule depends on**ionic character** of the amino acid side chains.

pH optimum varies for different enzymes:

- pH at which maximal enzyme activity is achieveddifferent for different enzymes
- Pepsin - digestive enzyme in the stomachmaximally active at pH 2
- other enzymes, designed to work at neutral pH**denatured** by such an acidic environment

MICHAELIS-MENTEN EQUATION

Reaction model

- Michaelis and Mentenproposed a simple modelaccounts for most of the features of enzyme-catalyzed reactions.
- enzyme reversibly combines with its substrateform an **ES complex**that subsequently breaks down to productregene rating the free enzyme

Michaelis-Menten equation

- Michaelis-Menten equation describes **how reactionvelocity varies with substrate concentration.**
- WhereVO = initial reaction velocity, Vmax = maximal velocity,Km = Michaelis constant = (k-1 +K2)/K1, [S] = substrate concentration
- following assumptions --made in deriving the Michaelis Menten rate equation:

1. Relative concentrations of E and S:

- concentration of substrate ([S])**much greater then**concentration of enzyme ([E]) so that thepercentage of to tal substrate bound by theenzyme **at any one time is small**.

2. Steady-state assumption:

- [ES] --does not change with time (the steady-state assumption),rate of formation of ES **is equal to** that of thebreakdown of ES

Important conclusion about Michaelis-Mentenkinetics

- **Characteristics of K**m:
  - Km - the michaelis constant - characteristic of an enzyme and its particularsubstratereflects the **affinity of the enzyme** for thatsubstrate.
  - equal to the substrate concentrationat whichreaction velocity is equal to ½ Vmax
  - **Km does not vary with the concentration ofenzyme.**
  - **Small Km:**
    - **A** numerically small (low) kmreflectsa **high affinity** of the enzyme for substratebecausea low concentration of substrate is needed to**half-saturate the enzyme** – that is, **reach avelocity that is ½ Vmax**
  - **Large Km:**
    - A numerically large (high) Kmreflects a low affinity of enzyme for substratebecausea high concentration of substrate is needed to **half-saturate the enzyme** – that is, **reach a velocity thatis ½ Vmax**

Relationship of velocity of enzymeconcentration:

- at all substrate concentrationsrate of the reaction**directly proportional** to the enzymeconcentration
- if the enzyme concentration is halvedinitial rate of the reaction (Vo), as well as that of Vmax **reduced** to one half that of the original.

Order of reaction:

- when [S] is much less than kmvelocity of the reactionapproximately **proportional** to the substrateconcentration
- rate of reaction is then said to be **first order** withvelocity is constant and equal to Vmax.
- **rate of reaction** is then independent of substrateconcentrationsaid to be zero order with respect to substrateconcent ration
- Lineweaver-Burk plotuseful for rapidly identifying important terms inenzyme kinetics, such as **Km and vmax.**
- y-intercept of such a graph is equivalent to
  - **inverse of vmax**;
  - x-intercept of the graph **represents 1/Km.**

REGULATION OF ENZYME ACTIVITY

- because the **intracellular level** of manysubstratesis in the **range of the Km.**
- Hence rates of most enzymesresponsive to **changes in substrateconcentration**
- an increase in substrate concentrationprompts an increase in reaction ratewhich tends to return the concentration of substrate towards normal
- some enzymes with specialized regulatory functionsrespond to
  - ✓ allosteric effectors or
  - ✓ covalent modification

- ✓ physiologic conditions

Allosteric binding sites

- Allosteric enzymesregulated by molecules called effectors (alsomodifiers)bind noncovalently at a site other than the active sitecomposed on multiple subunits
- regulatory site that binds the effectormay be located on a **subunit that is not itself catalytic**
- presence of an allosteric effectoralter the affinity of the enzyme for its substratemodify the maximal catalytic activit y of theenzyme
- Effectors that inhibit enzyme activitytermed **negative effectors**those that a increase enzyme activitycalled **positive ef fectors**.
- Allosteric enzymesusually contain multiple subunitsfrequently catalyze the **committed step early in apathway.**

Homotropic effectors:

- When the **substrate itself serves as aneffector**effect is said to be homotropic
- Most oftenan allosteric substrate functions as a positiveeffector
- In such a casepresence of a substrate molecule **at one site on theenzymeenhances** the catalytic properties of the oth er substratebinding sites**that is**their binding sites exhibit **cooperativity**
- These enzymes show a **sigmoidal curve**when**reaction velocity (V0) is plotted againstsubstrate concentration [S]**

Heterotropic effectors:

- effector may be different from the substratein which caseeffect is said to he heterotropic

Feedback inhibition

- by regulating the flow of substrate moleculesthrough the pathway that synthesizes that productprovides the cell wit h a product it needs
- Heterotropic effectors are commonly encountered**glycolytic enzyme** phosphofructokinasem **allosterically inhibited** by citratewhich is **not a substrate** for theenzyme

Regulation of enzymes by covalent modification

- Many enzymes may be regulated bycovalent modification
- most frequently by the the addition or removalof **phosphategroups** fromspecific **serine, threonine, ortyrosine** resid ues of the enzyme
- Protein phosphorylationrecognized as one of the **primary ways** in which cellular processes areregulated.

Phosphorylation and dephosphorylation:

- Phosphorylation reactionscatalyzed by a family of enzymes called proteinkinasesuse adenosine triphosphate (ATP) as a phosphatedonor
- Phosphate groupscleaved from phosphorylated enzymesby the action of phosphoprotein phosphatases

Response of enzyme to phosphorylation

- Depending on the specific enzymephosphorylated formmay be **more or less active** thanunphosphorylated enzyme**ph osphorylation**of glycogen phosphorylaseincreases activity
  of glycogen synthasedecreases activity

Induction and repression of enzymes synthesis

- regulatory mechanisms**modify the activity** of existingenzyme molecules.
- cells can also regulate the **amount of enzymepresent**usually by altering the rate of enzymesynthesisincreased (induc tion) or decreased(repression)
- Alterations in enzyme levels as a result ofinduction or repression of protein synthesisslow (hours to days),**allosteric ally regulated** change in enzymeactivityoccurs in **second to minutes.**

DMA'S CORNER OF WISDOM

INHIBITION OF ENZYME ACTIVITY

a) Competitive inhibition
b) Non- competitive inhibition
c) Allosteric inhibition

Reversible inhibitors

- bind to enzymes through noncovalent bonds]
- Dilution of the enzyme-
  inhibitor complex results in**dissociation of the reversibly bound inhibitor**recovery of enzyme activity.

Irreversible inhibition

- on dilution of enzyme-inhibitor complexinhibited enzyme **does not regain** activity
- two most commonly encountered types of inhibition
  - ✓ competitive
  - ✓ noncompetitive.

Competitive inhibition

- occurs **when the inhibitor binds reversibly**to the same site that the substrate wouldnormally occupy**competes with** t he substrate for that site.
- Effect on Vmax:by increasing [S].=effect of a competitive inhibitor – reversed
- At a **sufficiently high substrate concentration**reaction velocity **reaches the Vmax** observed in theabsence of inhibit or
- **Effect on Km:**
  - A competitive inhibitor**increases** the apparent Km for a given substrate.
  - This means thatin the presence of a competitive inhibitor**more substrate** is needed to achieve ½ Vmax.
- **Effect on Lineweaver-Burke plot:**
  - Competitive inhibition shows a characteristic Lineweaver-Burke plot
  - plots of the **inhibited and uninhibited reactions**intersect on the **y axis at 1/Vmax** (Vmax isunchanged).
  - plots of inhibited and uninhibited reactionsshow **different x axis intercepts** indicating that the apparent Km isin creased in the presence of the competitive inhibitor
- **Statins→examples of competitive inhibitors:**
  - antihyperlipidemic agents
  - **competitively inhibits** the first committedstep in cholesterolsynthesisreaction is catalyzed by hydroxymethylglut arylCoA reductase (HMG CoA reductase
  - Stain, drugssuch asatorvastatin &simvastatin**structural analogs** of the natural substrate for thisenzymecomplete effectively to **inhibit HMG CoA reductase.**
  - By doing sothey **inhibit de novo cholesterol synthesis** thereby**lowering** plasma cholesterol level

Noncompetitive inhibition

- inhibition is recognized by its**characteristic effect on Vmax**
- when the inhibitor and substrate bind **at different siteson the enzyme**.
- Noncompetitive inhibition occursnoncompetitive inhibitorbind either **free enzyme** or the **ES complex**thereby **preve nting** the reaction from occurring
- **Effect on Vmax:**
  - noncompetitive inhibition**cannot be overcome** by increasing theconcentration of substrate.
  - Thusnoncompetitive inhibitors **decreases the Vmax ofthe reaction.**
- **Effect on Km**
  - Noncompetitive inhibitors do not interferewith the binding of substrate to enzyme
  - Thus, the enzymeshows the same Km in the **presence or absence ofthe noncompetitive inhibitor.**
- **Effect on Lineweaver-burke plot**
  - Vmax-decrease in he presence of a noncompetitiveinhibitor
  - Km- unchanged
- **Examples of noncompetitive inhibitors:**
  - Some inhibitors act by **forming covalentbonds**with specific groups of enzymes.
  - For example**lead forms** covalent bonds with the sulfhdrylside chains ofcysteine in proteins.

- Ferrochelatasean enzyme that catalyzed the insertion of Fe2+into protoporphyrinexample of an enzyme sensitive to inhibition bylead
- examples of noncompetitive inhibition
  - ✓ insecticides-- neurotoxic effects
  - ✓ irreversible binding **at the catalytic site ofthe enzyme acetylcholinesterase**

Enzyme inhibitors as drugs

- Beta-lactam antibiotics, such aspenicillin and amoxicillinact by **inhibiting enzymes** involve in bacterial cell wall synthesis
- Drugs may also act by inhibiting extracellularreactionsangiotensin-converting enzyme (ACE)inhibitors.

Competitive	Non-competitive
○ Reversible	○ Reversible or Irreversible
○ Inhibitor resembles the substrate	○ No such resemblance
○ Inhibitor binds at the active site	○ Inhibitor does not bind the active site
○ **Vmax is constant**	○ **Vmax is lowered**
○ **Km is increased**	○ **Km is constant**
○ Inhibitor cant bind with enzyme-substrate (ES) complex	○ Inhibitor can bind with enzyme substrate (ES) complex
○ Affinity of the substrate to the enzyme is lowered	○ Enzyme substrate affinity is not changed.
○ Complex is [E-I]	○ Complex is [E-S-I] or [E-I]

Allosteric inhibition

- It is a mixed kind of inhibition where the inhibitor binds to the enzyme at a site other than the active site, called allosteric site.
- Does not follow Michaelis Menten hyperbolic kinetics. Instead it **gives a sigmoid kinetics.**

Examples of competitive inhibition:

Enzyme	Competitive inhibitor
• Lactate dehydrogenase	• Oxamate
• Aconitase	• Transaconitate
• Succinate dehydrogenase	• Malonate
• HMG-CoA Reductase	• HMG
• Dihydrofolate reductase	• Amethopterin
• Xanthine oxidase	• Allopurinol
• Folate reductase	• Methotrexate
• Mono amine oxidase (MAO)	• MAO inhibitors like amphetamine
• Acetyl choline esterase	• Physostigmine
Thus all competitive inhibitors are complex compounds and not simply metallic ions.	

Examples of allosteric inhibition:

Enzyme	Allosteric inhibitor	Allosteric activator
1. Glutamate dehydrogenase	• ATP, NADH	• ADP
2. Hexokinase	• ATP, G-6P	• ADP
3. Pyruvate carboxylase	• ADP	• Acetyl-CoA
4. Protein kinase	• -	• cAMP

Adenylyl cyclase

Stimulated by	Inhibited by
• ACTH,ADH, β- Adrenergics, Calcitonin, CRH, FSH, Glucagon, hCG, LH,LPH, MSH, PTH, TSH	• **Acetyl choline, α_2- Adrenergics** • **Angiotensin-II, Somatostatin**.

ENZYMES IN CLINICAL DIAGNOSIS

- Plasma enzymes can be classified into two major groups
  - ✓ a relatively **small group of enzymes**actively secreted into the blood bycertain cell typesliver secretes zymo gens (inactiveprecursors) of theenzymes**involved in** bloodcoagulation.
  - ✓ a **large number of enzyme species**released from cells during normal cellturnover.

○ **Alteration of plasma enzyme levels in disease states**

- tissue damage result inincreased **release of intracellular enzyme**into the plasma.activities of many of these enzymesroutinely determined for diagnosticpurposes in diseases of the **heart, liver,skeletal muscle**,elevated levels of ALT in plasmasignals possible damage to hepatic tissue.

○ **Isoenzymes and disease of the heart**

- Most isoenzymes (also called isozymes)enzymes that catalyze the same reaction**do not necessarily** have the same physicalpropertiesdifferences in amino acid sequenceisoenzymes may contain different numbers of chargedamino acids**separated from each other** by electrophoresisplasma levels ofcreatine kinase (CK), lactate dehydrogenase (LDH)determined in the diagnosis of myocardial infarction.
- **Quaternary structure of isoenzymes:**
  - Many isoenzymescontain **different subunits** in variouscombination.
  - creatine kinaseoccurs as three isoenzymes.
  - Each isoenzyme is a dimer composed of twopolypeptidescalled B and M subunitsassociated in one of three combinations
    - ✓ CK1 = BB
    - ✓ CK2 = MB
    - ✓ CK3 = MM.
  - Each CK isoenzyme shows a **characteristicelectrophoretic mobility**

Diagnosis of myocardial infarction:

- Myocardial muscleonly tissue that contains **more than five percent** of thetotal CK MB activity in plasma**virtually specific** for infarction of the myocardium
- Following an acute myocardial infarction,isoenzyme appears approximately **four to eight hours**following onset of chest pain**reaches a peak of activity** at approximately 24 hours
- Lactate dehydrogenase activityelevated in plasma following an infarctionpeaking 36 to 40 hours after the onset ofsymptomsdiagnostic value in patients **admitted morethan 48 hours** after the infarctiona time when **plasma CK2 mayprovide equivocal results**Troponin T and troponin Iregulatory proteins involved in myocardial contractility, released into the plasma **in response to cardiac damage**.
- Elevated serum troponinsmore **predictive of adverse outcomes** inunstable anginaormyocardial infarctionthan the conventional assayof CK2

Enzymes	Diagnostic Use
• Amylase, lipase	• Acute pancreatitis
• Lactate dehydrogenase (isozyme)	• Myocardial infraction
• Aspartate amino transferase (AST, or SGOT) • Alanine amino transferase (ALT or SGPT)	• Myocardial infraction • Viral hepatitis
• Ceruloplasmin	• Hepatolenticular degeneration (Wilson's disease)
• γ –Glutamyl transpeptidase	• Liver disease
• Creatinine kinase	• Muscle disorder, MI
• Acid phosphatase	• Metastatic Ca. of prostate
• Alkaline phosphatase	• Bone disorders, obstructive liver disease

ISOENZYMES

○ Isoenzymes are the physically distinct forms of the same enzyme that catalyze the same reaction, and differ from each other structurally, electrophoretically and immunologically.

- They differ in their physical properties because of genetically determined difference in amino acid sequence.
- They are separated by electrophoresis as they have different electrophoretic mobility.
- They have different Km value.

LDH Isoenzyme:

- **Isoenzyme LDH-1** with four 'H' subunit predominates in cardiac tissue, since heart expresses the H subunit almost exclusively.

LDH Isoenzymes			
Type	**Polypeptide chains**	**Electrophoretic mobility**	**Tissue rich in isoenzyme type**
• LDH-1	• (H4) H H H H	• Fast moving	• Found in myocardium
• LDH-2	• (H3M) H H H M		
• LDH-3	• (H2M2)H H M M		
• LDH-4	• (HM3) H M M M		
• LDH-5	• (M4) M M M M	• Slowest moving	• Found in liver (Hepatic)

Isoenzyme of lactate Dehydrogenase (LDH)

- Lactate dehydrogenase is a tetrameric enzyme & consists of four subunits.
- These subunits can occur in two isoform i.e.
  - ✓ H- isoform (for heart)
  - ✓ M- Isoform (for muscle)
  - All these isozymes though different physically they catalyze the same reaction of oxidation of LA to PA.
  - In normal serum, LDH2 (H3M) is the most prominent isoenzyme.

Creatinine phosphokinase exists as three isoenzymes in human tissue:

1. CPK-1 or CPK-BB: Found in Brain
2. CPK-2 or CPK-MB: Found in Myocardium
3. CPK-3 or CPK-MM: Found in skeletal muscle

- Creatinine phosphokinase-1 is essentially found in brain & ↑ed increased in brain ischemia.

Creatine phospho kinase (CPK) -2- CPKMB

- **Normally:**
  - CPK-2 (MB isozyme) occurs in very small quantity accounting for as less as 2% of total CK activity of plasma.
    - CKMB also exists in 2 form: $CKM\text{-}B_1$: Extra cardiac form/ $CKM\text{-}B_2$: Cardiac form
- **Myocardial infarction**
  - Elevation of CK-MB isoenzyme occurs **within 4 hours, maximum in 24 hrs, then falls rapidly**.
  - A ratio of $CKMB_1$: $CKMB_2$ above 1.5 is highly sensitive for the diagnosis of acute MI after 4-6 hours of onset of myocardial ischemia.

RATE LIMITING STEPS/KEY ENZYMES

• Cholesterol synthesis	• HMG CoA reductase
• Ketone body synthesis	• HMG CoA synthetase
• FA synthesis (lipogenesis)	• Acetyl CoA carboxylase
• Bile acid synthesis	• 7-α hydroxylase
• Gluconeogenesis	• Pyruvate carboxylase, Phospho Enol Pyruvate- Carboxykinase
• Glycogenesis	• Glycogen synthetase (dephosphorylated form)
• Glycolysis	• Phosphofructokinase
• Catecholamines synthesis	• Tyrosine hydroxylase
• Glycogenolysis	• Phosphorylase (phosphorylated form)
• Urea synthesis	• Carbamoyl transferase
• Krebs/TCA cycle	• Isocitrate dehydrogenase
• Uric acid synthesis	• Xanthine oxidase

COFACTORS & COENZYMES

Co-factors	Enzyme / Reaction
• **Zinc**	• **Superoxide dismutase*,Carbonic anhydrase *,**Glutamate dehydrogenase, Alcoholic dehydrogenase, **Alkaline phosphatase,** LDH (Lactate dehydrogenase), **δ-ALA dehydrogenase***
• **Magnesium**	• Carboxylase, **Transketolase*,** Phosphatase, Peptidase, Adenyl cyclase • Ribo nuclease , Kinase
• **Biotin**	• **Carboxylase***
• **Vitamin-C**	• **Hydroxylation***
• **Copper**	• **Tyrosinase *, Cytochrome oxidase*,** Amine oxidase, Superoxide dismutase
• **Pyridoxine**	• **Transamination ***
• **Molybdenum**	• **Xanthine oxidase ***
• **Selenium**	• **Glutathione peroxidase ***
• **Iron**	• Hemoglobin& Cytochrome
• **Manganese**	• Hydrolase *, Decarboxylase, Transferase

VITAMIN-B COMPLEX

Vitamin	Function	Deficiency	Special features
Vit B_1 (Thamine)	Cofactor for enzymes catalyzing -**Oxidation decarboxylation of α keto acid:** →Pyruvate dehydrogenase →α- keto glutarate dehydrogenase -**Transketolase reaction**	**Beriberi :** High cardiac output failure Na^+, H_2O retention Biventricular failure **Wernicke- korsakoff syndrome** (most common in alcoholics)	**Stored form:**Thiamine pyrophosphate * Its requirement increases in carbohydrate rich diet * Its deficiency is diagnosed by **↑in erythrocyte transketolase activity.**
Vit B_2 (Riboflavin)	→FMN and FAD are 2 co-enzymes and are **electron carriers** in oxidoreduction reaction. →Constituent of: # Cytochrome C- reductase # Warburg yellow enzyme # Fumarate dehydrogenase	• Seborrheic dermatitis • Angular stomatitis • Cheilosis	- Heat & acid resistant -Destroyed by light & alkali -Used as food additive because of its yellow color -Deficiency detected by measuring **RBC glutathione reductase**
Vit B_3 (Niacin)	→**NAD and NADP** are its active forms which operate as **hydrogen & electron transfer agent.** Deficiency seen in # Maize eater # Carcinoid syndrome # Hartnup disease	Pellagra # Diarrhea # Dermatitis # Dementia	→Synthesized from tryptophan **60 mg tryptophan = 1mg niacin** →High doses used to treat hyperlipidemia →In overdose causes cholestatic jaundice
Vit B_6 (Pyridoxine	→Coenzyme in **amino acid metabolism** mainly in: # Transamination reaction # Deamination #Decarboxylation → Deficiency can be induced by Isoniazide therapy. →[↑ **Kynurenine level in**	Epileptiform convulsion in infants Sideroblastic anemia	Required for synthesis of: *melanin *Heme precursor (δ amino levulinic acid) →In high does, causes sensory neuropathy, →B_6 is used in treatment of oxalate stone of kidney and Homocystinuria

	deficiency, converted to xanthuric acid, is a reliable criterion].		→**Tryptophan loading test** is done to detect its deficiency
Pantothenic Acid	→Part of co-enzyme A in : # Formation of acetyl COA # Formation of succinyl COA # Oxidation of fatty acid →As part of ACP (acyl carrier protein) in fatty acid synthesis	**Burning foot syndrome** G.I symptoms Changed sleep patterns.	
Biotin	Coenzyme in **carboxylation reaction**	Leiners disease Exfoliative dermatitis	Consumption of large amounts of raw egg white (which contains protein, **avidin** that binds biotin) can induce a biotin deficiency.
Vit B_{12} (cyancobal amine)	Cofactor for reactions: -Homocysteine → methionine -Methyl malonyl CoA → succinyl CoA	→Pernicious anemia (megaloblastic anemia) →Homocystinuria →Dementia →SACD (subacute cerebral degeneration)	→Found only in food of **animal origin** →Absorption requires two binding protein **Intrinsic protein**: secreted by partial cells of gastric mucosa **Cobalophillin**: In saliva
Folic acid	Tetrahydrofolate is a carrier of one carbon unit in synthesis of methionine, thymine and purine.	Megaloblastic anemia, Neural tube defect	reduces risk of neural tube defect & hyper homocystinemia

- **Thiamine acts as a coenzyme in following reactions:**
  a) **Oxidative decarboxylation of α-keto acids:**
  - **Pyruvate** —(Pyruvate dehydrogenase)→ Acetyl COA
  - Alpha ketoglutarate —(α-ketoglutarate dehydrogenase)→ Succinyl COA

  b) **Transketolase reaction:**
  Ribose-5 P+ xylulose 5-P —(transketolase)→ Sedoheptulose 7-P-Glyceraldehyde 3-P

- **Thiamine deficiency-** is diagnosed by an increase in erythrocyte transketolase activity observed after addition of thiamine pyrophosphate.

FOLIC ACID AND ONE- CARBON METABOLISM

- Some synthetic pathways require the addition of single carbon groups.
- These "**One-carbon units**" include **methane, methanol- formaldehyde, formic acid and carbonic acid** and can exist in a variety of oxidation states.
- It is possible to incorporate one carbon units at each of these oxidation states, **except methane**, into other organic compounds.
- These single carbon units can be transferred from carrier compounds such as **tetra hydro folic acid (TFH) and S-adenosyl methionine (SAM).**
- The "**One carbon pool" refers to single carbon units attached to this group of carriers**.

DMA'S CORNER OF WISDOM

VITAMIN B_{12} (CYANOCOBALAMINE)

Source and Absorption:

- Contains Cobalt. Found only in food of animal origin, not present in food of vegetables sources
- Absorbed from the distal third of ileum & requires it to be bound to highly specific glycoprotein **Intrinsic factor**, secreted by partial cells also called parietal factor.

Functions:

- **Catalyses the formation of** Tetra hydro folate from methyl H_4 folate
- **Homocysteine is converted into methionine** as the reaction proceeds**.**

Deficiency & Treatment:

- **In deficiency of Vit B_{12}**

Trapping of folate as methyl H_4 folate

↓

Tetrahydrofolate is not synthesized

↓

Impaired purine &pyrimidine synthesis

↓

Impaired DNA synthesis

↓

Prevent cell division & formation of nucleus of new RBCs

↓

Accumulation of megaloblast in bone marrow

↓

Megaloblastic anemia

- **Treatment:** Vit B_{12} & folic acid - increases DNA synthesis in bone marrow.

Reactions	Coenzymes
• Transketolation	• Thiamine (B1)
• Pyruvate dehydrogenase • α-ketoglutarate dehydrogenase complex	• Thiamine (B_1) • Riboflavin (B_2),Niacin (B_3) Lipoic acid
• Fatty acid oxidation: Succinate dehydrogenase • Succinate → Fumarate Lactate dehydrogenase • Lactate → Pyruvate	• Riboflavin (B_2) • Niacin (B_3)
Transamination &Deamination	Pyridoxine
• **Carboxylation** : • Acetyl CoA to Malonyl CoA • Propionyl CoA to Methyl malonyl CoA • Pyruvate to oxaloacetate	• Biotin

VITAMIN-A

Structure:

- Active forms are Retinol, Retinal and Retinoic acid.
- **Retinal is a component of visual pigment rhodopsin**.
- 1 mol β Carotene yields 2 moles of retinal.

Transport & storage:

- Dietary retinal is transported as retinyl esters in chylomicrons
- Stored form is retinyl esters mainly in liver & adipose tissue $\xrightarrow{Zn}$ mobilized form.

Functions:

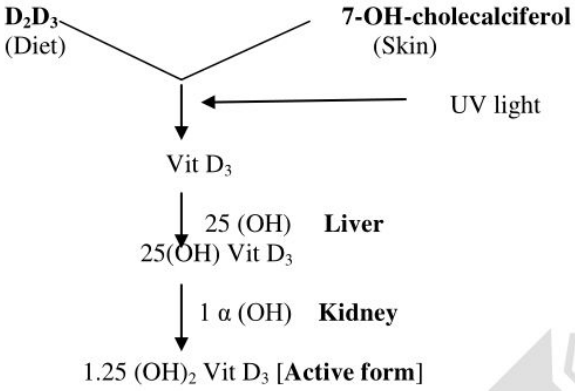
- Vision
- Maintenance of reproduction
- Anti infective
- Antioxidant
- Anticarcinogenic

Deficiency:

- Night blindness
- Xeropthalmia
- Growth retardation

VITAMIN-D (Anti-Rachitic vitamin)

Metabolism:



- **It a steroid hormone in the sense it binds to a nuclear receptor protein**.
- ↑ In absorption Ca^{2+} from gut ↑ mineralization of bone

Deficiency: Rickets (In children), Osteomalacia (In adults)

Toxicity:

- Vitamin D is most toxic of all vitamins.
- ↑ Serum Ca^{2+} ⟶ ↑ BP, Vaso constriction, Calcinosis [soft tissue calcification]
- Nausea ,Stupor
- Hypercalcemia & hyperphosphatemia

VITAMIN K

- **Post translation modification** of glutamate residue of precursor proteins to γ carboxy glutamate residue for generation of clotting factor.
  - ✓ **Vit K dependent clotting factors** are: Factor 2, 7, 9, 10& Protein C& S
- Vitamin K along with Vitamin C is required for synthesis of osteocalcin
- Haemorrhagic disease of newborn (HDN) is seen in Vit K deficiency.
- Vitamin K functions as a Coenzyme for carboxylase enzyme responsible for post translational modification of blood clotting factor.

$$\text{Glutamate} \xrightarrow[\text{Pyruvate carboxylase, Vitamin-K}]{CO_2} \gamma \text{ carboxy glutamate}$$

CLOTTING FACTORS

Factor: I- Fibrinogen

- It is a soluble plasma glycol-protein that consists of three non identical pairs of polypeptide chains, covalently linked by **disulfide bonds**.
- All the three chains are synthesized in the liver.

Factor: II-Prothrombin

- Single chain glycoprotein synthesized in the liver.

Factor: III – Tissue factor

Factor: IV- Calcium

Factor: V- Synthesized in liver, spleen, kidney & present in platelets, plasma [proaccelerin, labile factor].

Factor: VII- Proconvertin
Factor: VIII – Anti hemophilic factor-A
Factor: IX- Anti hemophilic factor-B [Christmas factor]
Factor: X- Stuart-power factor
Factor: XI- Plasma thromboplastin antecedent
Factor: XII- Hageman factor
Factor: XIII- Fibrin stabilizing factor

Vitamin deficiency	Neurological manifestation
• B_1 (Thiamine)	• Chronic peripheral neuritis • Wernicke's encephalopathy • Korsakoff's psychosis
• B_3 (Niacin)	• Dementia
• B_6 (Pyridoxine)	• Epileptiform convulsions in infants
• Pantothenate	• Burning foot syndrome
• Vitamin B_{12} (cyanocobalamine)	• Subacute combined degeneration (SACD)
• Folic acid	• Neural tube defects

ANTI-OXIDANTS

- To control and reduce lipid peroxidation, both humans in their activities and the nature invoke the use of anti-oxidants.
- **Anti-oxidants used as food- additives**:
  Propyl gallate, butylate hydroxyanisole (BHA) and butylated hydroxyl toluene (BHT).
- **Naturally occurring Anti- oxidants**:
  - Lipid soluble – Tocopherol (Vit-E)
  - Water soluble- Urate and Vit-C, Beta-carotene at low PO_2
- **Preventive anti- oxidants: (Reduces the rate of chain initiation**)
  Catalase, peroxidases like glutathione peroxidase, chelators of metal ions such as EDTA and DTPA.
- **Chain- breaking anti-oxidants (interfere with chain propagation):**Superoxide dismutase, urate, tocopherol.

OXIDATIVE STRESS & PREVENTION

- Several powerful oxidants are produced during the course of metabolism, in both blood cells and most other cells of the body.
- These include superoxide, hydrogen peroxide, peroxyl radicals and hydroxyl radicals and are collectively called **reactive oxygen species (ROS)**.
- Free radicals are atoms or group of atoms that have an **unpaired electron.**

REACTIONS OF IMPORTANCE IN RELATION TO OXIDATIVE STRESS

I) Reactions generating free radicals:

a) **Auto-oxidation of hemoglobin** to methemoglobin in RBC's (approximately 3% Hb is oxidized per day).
b) In other tissues, it is formed by the action of enzymes such as **cytochrome P 450 reductase and xanthine oxidase.**
c) By bacterial stimulation, neutrophils exhibit a respiratory burst and produce superoxide catalyzed by **NADPH OXIDASE.**

II) Reactions involving removal of free radicals:

a. Superoxide dismutase
b. Catalase
c. Myeloperoxidase
d. Glutathione peroxidase
e. Fenton reaction
f. Iron catalyzed Haber-Weiss reaction.
g. G6PD
h. Glutathione reductase.

Functions of plasma proteins

Function	Plasma proteins
• Anti- Proteases	• Antichymotrypsin ,α_1- Anti trypsin,α_2 – macro globulin, anti –thrombin
• Blood clotting	• Various coagulation factors, fibrinogen.
• Enzyme	• Coagulation factors, cholinesterase, amino transferases.
• Hormones	• Erythropoietin
• Immune defense	• Immunoglobulins • β_2 – microglobulin • complement proteins
• Inflammatory response	• Acute phase reactants (CRP, $\alpha_1$acid glycoprotein)
• Oncofetal	• α_1 – Fetoprotein (AFP)
• Transport or binding proteins	• **Albumin:** (Bilirubin, free fatty acids, calcium ions, metals like zinc, copper, steroids and other hormones, variety of drugs). • **Ceruloplasmin:** (copper) **Transcortin:** (cortisol binding globulin) • **Haptoglobin:** (binds extracellular Hb) **Lipoproteins** • **Hemopexin:** (binds heme) **Retinol binding protein** • **Sex-hormone binding globulin:** (binds testosterone, estradiol) • **Thyroid binding globulin:** (binds T_3, T_4) **Transferrin** • **Transthyretin:** (binds T_4 and forms a complex with retinol binding protein).

MORE ABOUT VITAMINS:

- **Dermatitis is seen with deficiency of :**
  - ✓ Pyridoxine (seborrheic)
  - ✓ Biotin
  - ✓ B_2, **B_3**,
  - ✓ Niacin (photo dermatitis)
- **Dementia is seen in deficiency of** :
  - ✓ Thiamine
  - ✓ Niacin
  - ✓ B_{12}
- **Angular stomatitis is seen in deficiency of :**
  - ✓ Riboflavin -
  - ✓ Niacin
  - ✓ Pyridoxine or iron
- **Tongue changes in vitamin deficiency**:
  - ✓ Riboflavin def. -------Magenta tongue
  - ✓ Niacin def. --------Beefy red tongue (fiery red tongue)
  - ✓ B_{12} def. ------ Baldness of tongue
  - ✓ Folic acid def. ----- Painful tongue
- Vit. Deficiency in pancreatic insufficiency: Vit. A
- Milling of rice cause loss of Thiamine (Vit. B_2 & protein also)Parboiling (Hot soaking) preserves them
- Riboflavin deficiency is almost always associated with pyridoxine deficiency.
- Mild hemolytic anemia is associated with Vit. E deficiency. Deficiency of Vit. E rarely occurs in newborn.
- Co-enzyme A synthesis requires Vit. B_6 & Co-enzyme A is active form of pantothenic Acid.
- Heat stable and light sensitive: Vit. K & B_2 (Riboflavin). Heat labile vitamins are Vit. C& Folic acid.
- Vit. A deficiency causes: Oro-oculogenital syndrome.

COMMONEST CLINICAL FEATURES OF MICRONUTRIENT DEFICIENCY:

- **Selenium**
  - Cofactor for Glutathione peroxidase.
  - Found to prevent Liver cell necrosis (Rich in garlic)
  - Def. caused keshan's disease and Kaschinbeck disease.
  - Anti-oxidant and cancer preventing property.
- **Zinc (Zn)**
  - Deficiency causes: Acrodermatitis enteropathica, impaired spermatogenesis Excess: Anemia, ARDS, pulmonary Fibrosis
- **Copper (Cu)**
  - Deficiency causes: Growth retardation, refractory hypochromic anemia, neutropenia, Subperiosteal hematoma, osteoporosis
  - Excess: Fanconi like syndrome, hemolytic anemia.
  - Inherited disorders of Cu. Metabolism:

- ✓ Wilson's disease
- ✓ Menke's disease – Sex linked-R neurodegenerative disorder due to Cu – deficiency. (Kinky/steel hair syndrome)

- **Chromium (Cr.):** Glucose tolerance factor, potentiator of insulin, deficiency causes hyperglycemia, glycosuria, peripheral neuropathy and encephalopathy
  - Se – deficiency, Cobalt-excess & Fe-excess causes cardiomyopathy
  - Manganese toxicity is associated with: Parkinsonism
  - Aluminum deficiency is associated with : Alzheimer's disease
  - Cd:-Ouch-Ouch disease
  - As & Thallium : Black foot disease.
- **Salient points:**
  - Zn-------Perioral pustular rash
  - Cu ------Microcytic anemia
  - Cr ------Hyperglycemia
  - Mn -----Dermatitis

2. CARBOHYDRATES

Calorific values of food products

Food stuff energy value [cal/g or Kcal//g]		
	In bomb calorimeter	In the body
• Carbohydrates	• 4.1	• 4
• Fat	• 9.4	• 9
• Protein	• 5.4	• 4

CLASSIFICATION OF CARBOHYDRATES

Monosaccharides — Oligosaccharides — Polysaccharides

Monosaccharides:

- Simplest of carbohydrates, referred as simple sugars.
- They cannot be further hydrolysed. They are in turn classified as:
  a. Based on functional group:
     - ✓ **Aldoses**: Aldehyde is the functional group e.g. glucose, glyceraldehyde.
     - ✓ **Ketoses**: Functional group is a keto group e.g. Fructose, dihydroxy acetone.

	ALDOSES [-CHO]	KETOSES [-CO]
• **TRIOSES**	• glycerose	• dihydroxyacetone
• **TETROSES**	• erythrose	• erythrulose
• **PENTOSES**	• ribose	• ribulose
• **HEXOSES**	• glucose	• Fructose

  b. Based on the number of carbon atoms:
     - ✓ Triose (3 carbon)
     - ✓ Tetrose (4C)
     - ✓ Pentose (5C)
     - ✓ Hexose (6C)

Oligosaccharides:

- Contain 2-10 monosaccharide molecules which are liberated on hydrolysis. They are further subdivided as:
  a. Disaccharides :
  On hydrolysis, they produce two molecules of the same or different monosaccharide
  Maltose → Glucose + glucose; Sucrose → Glucose + fructose; Lactose → Glucose + galactose
  b. Tri, tetra or penta saccharides etc.

Polysaccharides:

- Polymers of monosaccharide units with high molecular weight. They are of two types
- **Homopolysaccharides (homoglycans):**
  - ✓ Contain monosaccharide units of a single type e.g. starch, glycogen, insulin, cellular, dextrin and chitin.
- **Hetero polysaccharides (heteroglycans)**
  - ✓ They possess 2 or more different types of monosaccharide units or their derivatives (mucopolysaccharides) e.g. Heparin, chondroitin sulphate.

REACTIONS OF MONOSACCHARIDES

a. Tautomerization or enolization:

- Shifting a hydrogen atom from one carbon atom to another to produce enediols is known as tautomerization.
- Takes place in alkaline solution
- Glucose undergoes isomerization to form D- fructose and D- mannose- resulting in the formation of a common intermediate- the enediol

b. Oxidation:

- Depending on the oxidizing agents, the terminal aldehyde (or keto) or the terminal alcohol or both the groups can be oxidized
- For e.g. Glucose → oxidation of aldehyde group → Gluconic acid.
  - Oxidation of alcohol group → Glucuronic acid
  - Oxidation of both groups → Glucosaccharic acids

c. Reduction:

- Occurs when treated with reducing agents such as sodium amalgams. The products are
  - D- glucose → D- sorbitol
  - D- galactose → D-Dulcitol
  - D- Mannose → D- mannitol
  - D- Fructose → D- Mannitol + D- sorbitol
  - D- Ribose → D- Ribitol.

d. Dehydrogenase:

- Dehydrated by Conc.H_2SO_4
- Results in elimination of 3 water molecules
- Leads to formation of **furfural**
- Basis for **Molisch Test** i.e. Furfural + phenol → α- naphthol (coloured product)

e. Osazone formation:

- Occurs when reducing sugars are boiled with phenyl hydrazine in acetic acid.

f. Ester formation:

- Esterification of carbohydrates with phosphoric acid is a common reaction in metabolism.

DISACCHARIDES

- **Most common oligosaccharides**
- Consists of 2 monosaccharide units held together by a glycosidic bond.
- They are water soluble and sweet to taste.
- They are of 2 types:

a. **Reducing disaccharides** (disaccharides with free aldehyde or keto group)

Maltose: → Malt sugar made of 2 glucose units,
→ Produced by the digestion of starch by pancreatic amylase.

Lactose → milk sugar, composed of β- D glucose and β –D- galactose held together by β (1→4)glycosidic bond
→ hydrolysed by lactase

b. **Non-reducing disaccharides :** (Disaccharides with no free group)

E.g. Sucrose → (**cane sugar, invert sugar**) made of α-D glucose & β –D fructose trehalose.

MUCOPOLYSACCHARIDES

- Commonly known as glycosaminoglycans (GAG)
- They are heteroglycans made up of repeating units of sugar derivatives, mainly amino sugars and uronic acids.
- Some of them are found in combination with proteins to form mucoids or mucoproteins or proteoglycans.
- They are essential components of tissue structure.Some of them are:

Mucopolysaccharides	Made of	Features
• Hyaluronic acid	• D- glucuronic acid + N-Acetyl glucosamine	• Presents in synovial fluid and vitreous humor.
• Chondroitin 4- sulfate	• D- glucuronic Acid + N-acetyl galactosamine 4- sulfate	• Constituent of bone cartilage, tendons, heart valves, skin, cornea etc.
• Heparin	• D- glucuronate 2sulfate + N-sulfo glucosamine -6 sulfate	• Anticoagulant
• Dermatan sulfate	• L-iduronic acid + N-Acetyl galactosamine 4-sulfate	• Present in skin
• Keratan sulfate	• D- galactose + N- Acetyl glucosamine 6 sulfate	• -

DMA'S CORNER OF WISDOM

PROTEOGLYCAN

- Core is made of protein
- 95 percent carbohydrate and 5 percent protein
- They are negatively charged
- They are linear (long and unbranched) chain
- They hold a large amount of water
- They repel each other as they are negatively charged thus occupying a lot of space
- Example - gel

GLYCOPROTEIN

- They are branched chain
- <85 percent carbohydrate and the rest is proteins
- Examples
  - Surfactant
  - TSH
  - Blood proteins except albumin
  - Beta-Hcg

MAJOR METABOLIC FEATURES OF SPECIFIC ORGANS

Organ	Major pathways	Main substrates	Major products exported	Specialist enzymes
Liver	Glycolysis, gluconeogenesis, lipogenesis, β-oxidation, TCA cycle, ketogenesis, lipoprotein metabolism, drug metabolism, Synthesis of bile salts, urea, uric acid, cholesterol, plasma proteins.	FFA, glucose, lactate, glycerol, fructose, amino acids, alcohol	Glucose, triacylglycerol in VLDL, ketone bodies, urea, uric acid, bile salts, cholesterol, plasma proteins.	-Glucokinase -Glucose-6-phosphatase -Glycerol kinase -Phosphoenol Pyruvate carboxy kinase -Fructokinase -Arginase -HMG CoA synthase -HMG CoA lyase -Alcohol dehydrogenase
Brain	Glycolysis, amino acid metabolism, neurotransmitter synthesis	Glucose, amino acids, ketone bodies in prolonged starvation	Lactate, end products of neuro transmitter metabolism	Enzymes of neuro transmitter synthesis & metabolism
Heart	β-oxidation, TCA cycle	Ketone bodies, FFA, lactate, chylomicrons & VLDL, some glucose	-	Lipoprotein lipase, very active ETC
Adipose tissue	Lipogenesis, esterification of fatty acids, lipolysis in fasting	Glucose, triacylglycerol in VLDL & Chylomicrons	FFA, glycerol	Lipo protein lipase, hormone sensitive lipase, enzymes of HMP shunt
Fast twitch muscle	Glycolysis	Glucose, glycogen	Lactate (Alanine & keto acids in fasting)	-
Slow twitch muscle	β-oxidation and citric acid cycle	Ketone bodies, chylomicrons, and VLDL triacyl glycerol	-	Lipo protein lipase, very active electron transport chain
Kidney	Gluconeogenesis	FFA, lactate, glycerol, glucose	Glucose	Glycerol kinase, phosphoenol Pyruvate carboxy kinase

RBCs	Anaerobic glycolysis, HMP shunt	Glucose	Lactate	Hb, enzymes of HMP shunt

GLUCOSE TRANSPORTERS

- GLUT 1: RBC , fetal tissue, endothelial cells of barrier tissue
- GLUT 2: renal tubular cells, small intestine, liver cells, B- cells of pancreas
- GLUT 3 : neurons & placenta
- **GLUT 4** : Adipocytes, & striated muscle [found in CVS & skeletal] - **Insulin dependent**
- GLUT 5 : sperm, kidney, testes and intestine
- GLUT 6 : WBC and spleen

KEY POINTS ON GLUT

- Glut 1 & 3 : high affinity for glucose [low Km] & normal conditions = peak Vmax
- Glut 2 : Low affinity for glucose [high Km], B cells of pancreas have Glut 2 receptors for recognition of glucose therefore release "insulin".
- Glut 4 : insulin dependent. increase glucose level = increase GLUT 4 on membrance receptors via exocytosis.

Pathways of the Carbohydrate System:

- **Glycolysis**: splits glucose to pyruvate, which can be converted to lactate.
- **Gluconeogenesis**: converts pyruvate to glucose.
- **Glycogenesis**: synthesis of glycogen, carbohydrate fuel storage form.
- **Glycogenolysis**: breakdown of glycogen.
- **Pentose Phosphate Pathway (PPP)**: produces NADPH for cell biosynthesis.
- **Citric Acid Cycle**: converts Acetyl CoA to CO_2 and ENERGY

GLYCOLYSIS

- **Glycolysis**: pathway for all mammalian cells for the metabolism of glucose (or glycogen) to pyruvate and lactate.
  - In glycolysis glucose (C_6) is converted into 3C units substances; Pyruvate (C_3) and lactate (C_3)
  - **All the enzyme of glycolysis are present in Cytosol**
  - This is not a complete breakdown of glucose as pyruvate further enters mitochondria to completely degraded into CO_2 and H_2O
  - It is unique in the sense that it can **function either aerobically or anaerobically**.
  - Under **aerobic conditions, pyruvate** is the final product whereas in **anaerobic conditions, lactate** is formed as a final product.
- **A committed step** - Irreversible reaction which commits the product for a particular metabolism.
- There are three steps in glycolysis that are physiologically irreversible.

1. Glucose —(Glucokinase / Hexokinase)→ Glucose-6-PO_4
2. **Fructose -6-Phospate** —(**Phosphofructokinase**)→ **Fructose1,6-bisphosphate**
3. Phosphoenol pyruvate —(Pyruvate kinase)→ Pyruvate

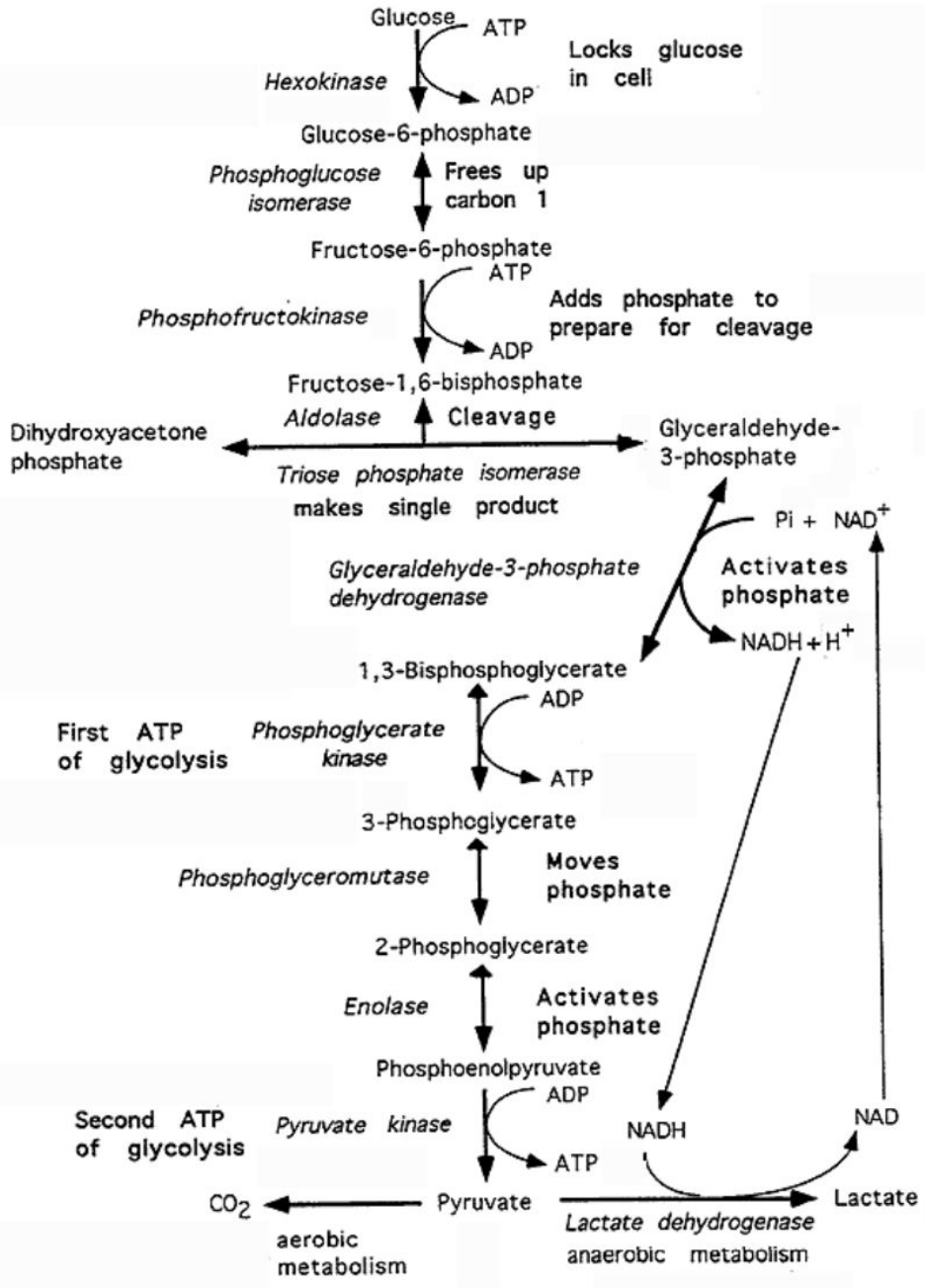
- **Rate limiting step: catalyzed by Phosphofructokinase (PFK-1)**
- **Cancer cells** derive nutrition from glycolysis. The tumor cells have to depend on anaerobic process- glycolysis for ATP .

ENERGY YIELD FROM GLYCOLYSIS

- Despite the production of some ATP during glycolysisend products, pyruvate or lactatestill **contain most of the energy** originally contained inglucose
- **TCA cycle is required** to release that energycompletely
- **Anaerobic glycolysis:**

- ✓ Two molecules of ATPgenerated for each molecule of glucoseconverted to two molecules of lactateno net production or consumption of NADH
- ✓ Anaerobic glycolysisalthough releasing only a small fraction of theenergy contained in the glucosemoleculea valuable source of energy under several condition,includingWhen the oxygen supply is limitedas in muscle during intensive exercise;for tissues with few or no mitochondria, such asmedulla of the kidneymature erythrocytesleukocytes,cells of the lens, cornea, and testes.

- **Aerobic glycolysis:**
  - ✓ direct formation and consumption of ATPsame as in anaerobic glycolysisa **net gain of two ATP** per molecule ofglucose.
  - ✓ **Two molecules of NADHproduced per molecule** of glucosethree ATP for each NADH molecule entering the chain



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